13

INDUCTION OF NEUROTROPHIC ACTIVITY BY TUMOR NECROSIS FACTOR IN CULTURED CELLS. X. He, C. Lu. Department of Neurobiology, Second Medical University, Shanghai, P.R. China.

Tumor necrosis factor (TNF) is a multipotent cytokine which is now known to be implicated in diverse biological processes such as endotoxic shock, inflammation, immunoregulation, antiviral defense, etc. Recently it was reported that TNF could, synergistically with IL-1 and IFN-γ, stimulate the synthesis of nerve growth factor (NGF) in fibroblasts. In the present study we observed that the addition of TNF at a concentration of 1 ng/ml can induce neurotrophic activity to the dorsal root ganglial neurons of embryonal chicken in the medium of cell cultures of Hela (epithelial line derived from cervical carcinoma), WISH (epithelial line derived from human amnion), U937 (a histiocytic lymphoma line) and KG-1 (a premyelolytic leukemia line). Analysis of NGF gene expression in these cell lines by Northern blot revealed that Hela and WISH had NGF mRNA expression after triggered by TNF, but there was no NGF mRNA expression in U937 and KG-1 with or without TNF treatment. Therefore the induced neurotrophic activity in the medium of cell cultures by TNF may be mediated through NGF or other substances.

CRF

14

EXPRESSION OF A NOVEL RECEPTOR FOR CORTICOTROPHIN-RELEASING FACTOR (CRH-R2) IN PERIPHERAL TISSUES OF THE MOUSE AND IN THE ATRIAL CARDIOMYOCYTE CELL LINE, AT-1. K.A. Heldwein, P. Stenzel,§ M.B. Rittenberg, M.P. Stenzel-Poore. *Department of Molecular Microbiology and Immunology, §*Department of Pathology, Oregon Health Sciences University, Portland, OR 97201.

Corticotrophin-releasing hormone (CRH) is a 41-amino acid peptide which functions as the principal mediator of the stress response in mammals. CRH stimulates production of adrenocorticotropic hormone (ACTH) via specific CRH receptors located on pituitary corticotropes. In addition to pituitary and brain effects CRH has been found to have peripheral effects involving the immune and cardiovascular systems. We have identified a novel CRH receptor (CRH-R2) that is strongly expressed in the heart and skeletal muscle but only weakly in the brain. A brain/pituitary form of CRH receptor (CRH-R1) has previously been reported which, in contrast to the cardiac receptor (CRH-R2) is highly expressed in the brain but is virtually absent in peripheral tissues. The two CRH receptors show significant sequence homology (69%) and are members of the seven transmembrane G-protein coupled secretin receptor family Functional studies using CRH-R2 transfected cells indicate that CRH and the CRH-related amphibian peptide, sauvagine, bind with high affinity to CRH-R2 and stimulate intracellular accumulation of cAMP. Interestingly, sauvagine bound CRH-R2 with an affinity 50-fold higher than CRH, an important finding in light of sauvagine's greater potency in mediating hypotensive effects in the peripheral vascular system. To investigate the role of CRH in cardiac signaling in vitro, we have identified a cardiomyocyte cell line (AT-1) that expresses high levels of CRH-R2 and lacks CRH-R1. Since AT-1 cells have been shown to retain many physiological properties of normal atrial myocytes, this cell line should provide a powerful in vitro cell model to investigate the cardiac effects of CRH and thereby elucidate new pathways in the cardiovascular response to stress. In conclusion, we have identified a novel CRH receptor that is highly expressed in the heart and skeletal muscle; the distribution of this receptor in peripheral tissue and its sensitivity to CRH and sauvagine suggest that CRH-R2 rather than CRH-R1 mediates the hypotensive effects of these hormones.

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